Viral Blips After Treatment Initiation During Acute Human Immunodeficiency Virus Infection

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Transient viral blips ≥20 copies/mL were observed in 16.9% of acutely treated adults with HIV. Blip incidence increased from 0.0 (95% CI, 0.0–2.9)/100 person-years after ART in Fiebig I to 15.9 (7.6–29.2) in Fiebig V. Increasing viral load and Fiebig stage at ART initiation were independently predictive of blips.

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The primary goal of antiretroviral therapy (ART) is to achieve and maintain suppression of peripheral human immunodeficiency virus (HIV), ideally below the limit of detection. Transient low-level viremias, or blips, are observed in up to 50% of individuals receiving otherwise suppressive ART initiated during chronic HIV infection [1]. Many blips reflect random biological fluctuations, statistical variations, and HIV RNA assay variability [2, 3]. However, blips may also represent production of viral particles following stochastic activation of viral production from stably established reservoirs [4, 5].

As compared with chronic infection, ART initiation during acute HIV infection (AHI) limits reservoir establishment, enhances reservoir decay, restricts viral genetic diversification, improves HIV-specific immune responses, and may facilitate sustained viral suppression after ART cessation [6]. Early ART initiation may also impact the occurrence of blips [7].

We hypothesized that earlier ART initiation during AHI might reduce the frequency of blips.

METHODS

The ongoing RV254/SEARCH010 cohort (clinicaltrials.gov NCT00796146) enrolls adults diagnosed with AHI upon presentation for HIV screening at the Thai Red Cross Anonymous Clinic. Acute HIV infection is defined by either a nonreactive fourth-generation immunoassay with a positive nucleic acid test or reactive fourth-generation immunoassay with a nonreactive second-generation immunoassay [8]. Participants are offered ART via a separate protocol (clinicaltrials.gov NCT00796263). Participants who enrolled from May 2009 to May 2017, initiated suppressive ART with confirmed HIV RNA of less than 20 copies/mL, and continued ART for at least 1 year were included in these analyses.

Participants underwent plasma HIV RNA quantification at enrollment; study weeks 2, 4, 8, and 12; and every 12 weeks thereafter. All samples were tested using the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test v2.0 (Roche Diagnostics) with a lower limit of quantification of 20 copies/mL. After achieving viral suppression, a blip was defined as any HIV RNA of 20–999 copies/mL immediately preceded and followed by HIV RNA of less than 20 copies/mL without a change in ART. Multiple measurements within 30 days that would otherwise satisfy blip criteria were considered a single blip and the highest measurement recorded as the magnitude. Persistent low-level viremia was defined as 2 or more consecutive HIV RNA measurements of 20–999 copies/mL at least 30 days apart. Confirmed HIV RNA of 1000 or more copies/mL was considered viral failure.

Participants were stratified by whether or not they experienced any blips during observation and compared using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. Blip frequency was defined as the number of blips divided by the amount of observation time on otherwise suppressive ART. The chi-square test for trend was used to test the hypothesis of a linear association between Fiebig stage and blip frequency. Negative binomial regression was used to calculate rate ratios (RRs) and 95% confidence intervals (CIs) for associations of participant characteristics at ART initiation with blip frequency. Observation time was censored upon persistent low-level viremia, first viral failure, ART cessation, study withdrawal, enrollment into an interventional substudy, death, or loss to follow-up. Fiebig stage and factors that were

significant ($P < .05$) in unadjusted models were included in the multivariable model. Blip magnitude was explored using Dunn's pairwise comparisons to evaluate differences across Fiebig stages and Spearman's ρ correlation to evaluate associations with duration of viral suppression. Analyses were performed using GraphPad Prism 7.0 (GraphPad Software) and Stata 15.0 (StataCorp LP).

The study was approved by institutional review boards at Chulalongkorn University, Bangkok, Thailand; Walter Reed Army Institute of Research, Silver Spring, Maryland; and all participating institutions. All participants provided written informed consent prior to enrollment.

RESULTS

From 213 589 samples screened, 468 participants were enrolled during AHI, including 87 who were excluded from these analyses due to viral load testing with a different platform, 52 due to ART use for less than 1 year after viral suppression, and 3 for failure to achieve viral suppression. A total of 326 participants satisfying inclusion criteria for these analyses were monitored for blips over a median of 2.4 (interquartile range [IQR], 1.8–3.4) years after achieving viral suppression. Participants had a median age of 26 (IQR, 22–31) years and 305 (93.6%) were men who have sex with men.

Fifty-five (16.9%) participants demonstrated 69 blips with an incidence of 8.2 (95% CI, 6.4–10.4) per 100 person-years. Compared with participants without blips, those who experienced blips had a lower CD4 count (median [IQR], 308 [246–460] vs 379 [275–507] cells/mm³; $P = .018$), higher HIV RNA (median [IQR], 6.6 [6.0–7.0] vs 5.8 [5.2–6.6] $\log_{10}$ copies/mL; $P < .001$), and were more likely to be in later Fiebig stages at ART initiation ($P = .001$). The 2 groups did not differ by age, HIV risk group, education, HIV subtype, or initial ART regimen (Supplementary Table 1).

The median time from first undetectable HIV RNA to a blip was 60 (IQR, 37–109) weeks. This was significantly shorter among participants treated during Fiebig II (35 [IQR, 22–60] weeks) compared with Fiebig III (65 [IQR, 47–137] weeks) ($P = .024$). Other pairwise comparisons between Fiebig stages were not significant.

The rate of blips was lowest among participants who initiated ART during Fiebig I (0.0 [95% CI, 0.0–2.90] per 100 person-years) and highest among those who initiated ART during Fiebig V (15.9; 95% CI, 7.6–29.2) (Figure 1A) ($P < .001$ for test of trend). The magnitude of the 69 observed blips was a median of 33 (IQR, 23–50) copies/mL. Only 16 (23.2%) were greater than 50 copies/mL, including 4 (5.8%) greater than 100 copies/mL and none greater than 200 copies/mL (Figure 1B). There were no statistically significant differences in blip magnitude by Fiebig stage and no association between duration of antecedent viral suppression and blip magnitude.

In unadjusted negative binomial regression models, HIV RNA and Fiebig stage at ART initiation were significantly associated with increasing frequency of blips (Supplementary Table 2). In the multivariable model, HIV RNA of more than 1 000 000 copies/mL at ART initiation was associated with 4.39 (95% CI, 2.32–8.30) times as many blips as HIV RNA of 1 000 000 or fewer copies/mL ($P < .001$). Compared with ART initiation during Fiebig I/II, increasing frequency of blips was observed in participants who initiated ART during Fiebig III/IV (RR, 1.87; 95% CI, 0.95–3.68; $P = .07$) and Fiebig V (RR, 4.20; 95% CI, 1.57–11.25; $P = .004$).

DISCUSSION

We observed an increased frequency of blips with ART initiation at later Fiebig stages. Prior data have suggested that blip frequency may be directly correlated with HIV reservoir size [9]. The HIV reservoir expands rapidly during AHI and it is possible that increased size of the intact proviral reservoir at later Fiebig stages could contribute to intermittent low-level viremia [10]. Mathematical models support a hypothesis that blips are caused by stochastic reactivation events from latently infected cells and it follows that a larger latent reservoir would therefore yield a greater frequency of blips [5].

We observed blips of 20 or more copies/mL at a lower rate than has been described for blips of 50 or more copies/mL in adults who initiated ART during chronic HIV infection in Canada (11 blips/100 person-years) [1], Washington state (19.4 blips/100 person-years) [11], and Europe (37.4 blips/100 person-years) [12]. Prior studies that included individuals who initiated ART within 6 months of estimated seroconversion described blips of more than 50 copies/mL in 13% of participants over a median of 16 months [13] and half as many blips as compared with participants who initiated ART during chronic infection [7]. Taken together, these findings suggest that ART initiation during AHI reduces the frequency of blips.

Blips were also of generally low magnitude in our study. After ART initiation during chronic infection, over 85% of blips are less than 200 copies/mL and risk of later viral rebound is increased predominantly with blips of 500 or more copies/mL [1]. All blips in our study were less than 200 copies/mL; transmission events at this level are unlikely [14] and most guidelines do not recommend any change in clinical management based on even sustained viremia of less than 200 copies/mL [15].

As has been observed in individuals who initiated ART during chronic infection, higher HIV RNA at ART initiation was predictive of blips in our study [1, 11]. Plasma HIV RNA at ART initiation is also directly correlated with reservoir size [16], supporting the hypothesis that blip frequency reflects the size of the pool of latently infected cells.

Our study characterized blips in a large cohort of adults who initiated ART during AHI, including many in the earliest Fiebig
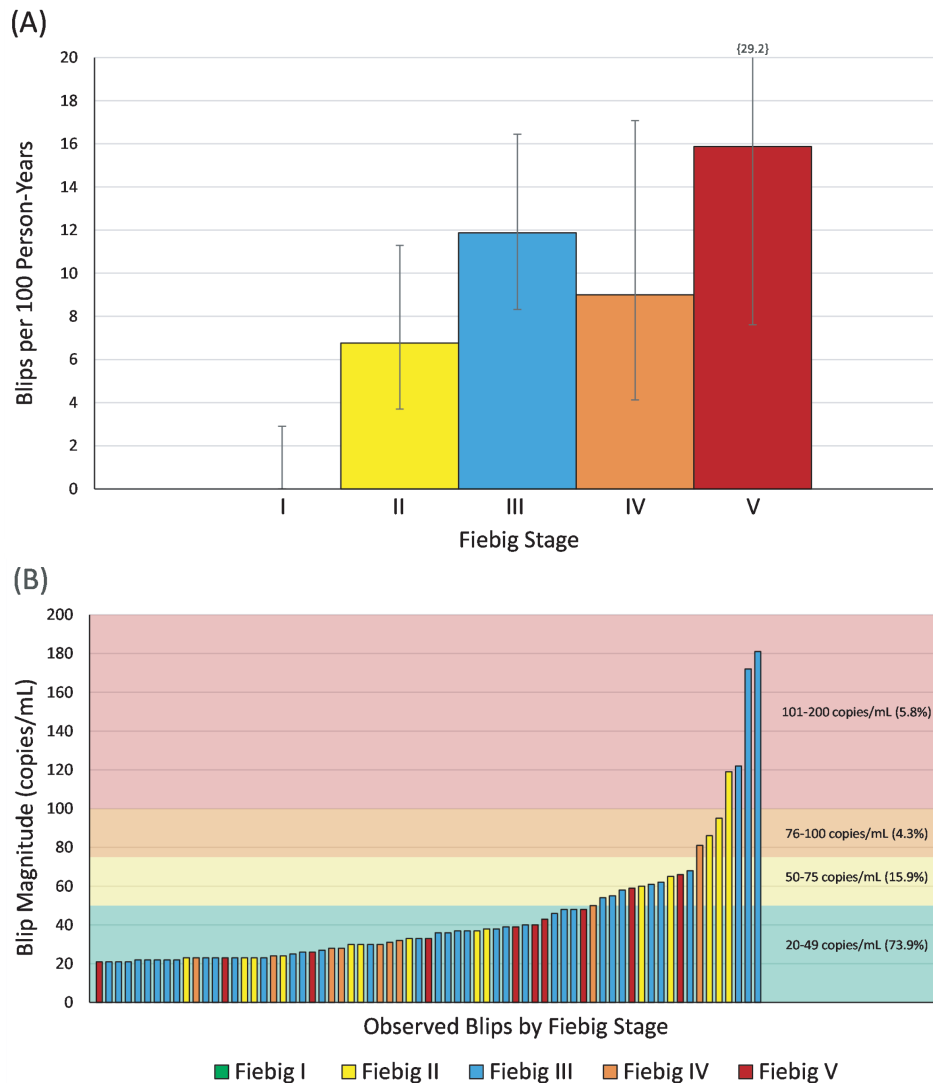
Figure 1. Frequency and magnitude of viral blips by Fiebig stage. A total of 69 blips ≥20 copies/mL were observed among 55 participants. The rate of blips stratified by Fiebig stage with 95% confidence intervals is presented in panel *A*. The magnitude of each individual blip is indicated in panel *B* alongside percentages observed in various magnitude categories of interest. The study population included participants who initiated antiretroviral therapy during the following Fiebig stages: Fiebig I, 46 (14.1%); Fiebig II, 79 (24.2%); Fiebig III, 131 (40.2%); Fiebig IV, 44 (13.5%); and Fiebig V, 26 (8.0%).

stages. Since some blips may reflect variability of test performance characteristics, a strength of our study was the consistent use of 1 HIV RNA assay [3]. However, because blips were relatively rare, only limited statistical exploration of predictors could be performed and clinical outcomes associated with blips could not be assessed. Data evaluating HIV reservoir size and characteristics were not available for most participants in these analyses. Findings from this cohort of predominantly Thai men with HIV subtype CRF01_AE and engaged in a highly structured research protocol may not be generalizable to other populations in routine clinical care.

In conclusion, viral blips occurred in a minority of participants and had a generally low magnitude after treatment initiation during AHI. Earlier ART initiation reduced the frequency of blips, but the clinical implications of this remain uncertain. As with ART initiation during chronic infection, viral load at treatment initiation was also a strong predictor of blips. Further research is needed to evaluate associations with viral reservoirs, intact proviruses, and clinical outcomes.

Supplementary Data

Notes

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